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IPAC-RS Comments on the Draft Guidance for Industry and Food and Drug Administration Staff on "Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products" Docket No. FDA-2015-D-1659

On behalf of the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), please find enclosed comments on the FDA Draft Guidance "Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products."

IPAC-RS is an international association that seeks to advance the science and regulatory science of orally inhaled and nasal drug products (OINDP) by collecting and analyzing data and conducting joint research and development projects. Our members include innovator and generic companies that develop, manufacture or market orally inhaled and nasal drug products for local and systemic treatment of a variety of debilitating diseases such as asthma, chronic obstructive pulmonary disease and diabetes. IPAC-RS aims to build consensus and contribute to effective regulations and standards by sharing the results of our research through conferences, technical journals and discussions with regulatory bodies.

IPAC-RS commends the U.S. Food and Drug Administration for drafting this guidance and appreciates your consideration of the comments provided on the following pages, which include both general and specific comments.

General Comments

IPAC-RS agrees with the principles that (i) better understanding of which elements of the CMC information constitute established conditions could allow for a more effective post-approval submission strategy and (ii) clarity on what constitutes an established condition could provide regulatory pathways to better regulate post-approval changes by utilizing flexibility and risk-based principles. In particular, IPAC-RS very much welcomes FDA's recognition that 'demonstration of risk mitigation within the application can allow for greater operational flexibility for certain parameters typically considered established conditions.'

IPAC-RS supports the notion that the control strategy is a key component of the established conditions, and that this will most likely evolve and need to be updated over a product's life cycle as knowledge is gained. FDA's clarification of which elements of the control strategy are submitted in an application and may be considered established conditions is helpful, as is FDA's explanation of control strategy elements generally *not* considered established conditions (i.e., lines 183-190). Additionally, the proposal to present a summary of the established conditions in a tabular format in the submission is a pragmatic approach.

IPAC-RS notes, however, that the content of this guidance will have implications for global regulatory submissions. As such, IPAC-RS would value FDA feedback on how industry could apply concepts in this guidance along with concepts addressing similar topics, expected to be in ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle*

Management. IPAC-RS would welcome guidance on how industry might progress forward within the context of both guidelines. This will be important with respect to specific requirements, such as proposals for location of the established conditions summary in the CTD. Further, the ICH Q12 may provide an effective mechanism for making recommendations on established conditions that could be applied in both ICH and non ICH regions."

Finally, IPAC-RS has concerns about the proposed level of detail on the manufacturing process description that should constitute an established condition; designating non-critical process parameters as established conditions is particularly problematic.

We greatly appreciate this opportunity to provide comments to FDA on this guidance, and FDA's efforts on the document. Please do not hesitate to contact us with questions.

Sincerely,

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Specific Comments

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Page 1, I / 32-34	It appears that the new guidance would be mandatory for all new CTDs (NDA/BLA). Approved legacy products are excluded but it is acknowledged that additional guidance are under preparation (line 236-238)	Include clarifying language that permits sponsors to submit original CTDs with limited established conditions in support of new drug products.	Experience which is not yet available at the time of original CTD submission may be needed to know exactly what level of detail can be designated as established condition or not. An alternative approach, particularly for those programs in which additional data development is anticipated such as breakthrough therapy and biotechnology products, could be useful to both sponsors and FDA as a means to facilitate dossier review. Subsequent agreement on established conditions for this type of dossier submission could be covered by the expected new guidance addressing legacy products.	Moderate
Page 4, III.A/140-144	The controls can include parameters and attributes related to drug substance (DS), excipients, in-process materials, drug product (DP) materials, inclusive of small and large molecule products, facility and equipment operating conditions,	Recommending modifying the third sentence to: “The controls can include, for example, various parameter and attributes related to items...”	The examples of controls listed are not exhaustive, and it would be helpful to introduce some text here to clarify this.	Information or requiring clarification

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	in-process controls, finished product specifications, and the associated methods and frequency of monitoring, sampling, testing, and control, etc.			
Page 5, III.B/ 154-167	• DS/DP (including in-process materials) manufacturing and testing facilities. • Source of and specifications for starting materials for biological products. • Process, including in-process tests and sequence of operations, equipment; and process parameters and their ranges. • Specifications, including the tests, analytical procedures and acceptance criteria; including specifications for the DS, other components, in-process materials, and the DP. • Container closure system, components, and specifications. • Maintenance strategy for chemometric and/or multivariate models (e.g., for models that may have a high impact on product quality).		There may be value in presenting the bulleted items for control strategy elements, in lines 154 – 167, in a table that could be referenced throughout the guidance, as needed.	Information or requiring clarification

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Page 5 III.B/168-169	Graphic in guidance	Consider revising or deleting the schematic.	The schematic is misleading and would value from further consideration.	Information or requiring clarification
Page 6 III.B / 183-190	Although a control strategy is generally supported and verified by elements listed below, these elements are not generally considered established conditions: • Batch records • Development data • Characterization data • Validation data • Batch analysis data	Reword lines 183-184 as follows: "A control strategy is generally supported and verified by elements listed below, which are included in a submission to justify the established conditions but are not in themselves considered established conditions"	The text is vague and subject to interpretation. Consider rewording this main text to avoid any confusion and the potential for misinterpretation of the intent.	Critical
Page 6, III.B / 183-190 Footnote 13	The batch record should reflect the current manufacturing process and the associated in-process parameters and controls needed to ensure product quality and performance. It is not expected that all changes to a batch record would be reported to FDA, but if there is a change to the control strategy that impacts the batch record, a current batch record should be provided in the appropriate regulatory submission. Refer to 314.50(d)(1)(ii)(c) and 314.94(a)(9) for associated regulations about batch record	Suggest rewording as follows: ".....but if there is a change to a control strategy that impacts how established conditions are described in the batch record, a current batch record should be provided..."	The bullet states that batch records are not generally considered established conditions, but Footnote 13 states that "if there is a change to a control strategy that impacts the batch record, a current batch record should be provided..." In practice this could be interpreted as meaning that even revisions to control strategy elements not defined as established conditions in the application would still need to be reported to FDA via the updated batch record. IPAC-RS assumes this is not the intent. Suggest that this footnote is	Critical

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	submission.		reworded to improve clarity.	
Page 6, IV.A, 204-205	The relevant information would still be considered an established condition even if it is located in a CTD section not specified below.		Please provide clarification regarding what is meant by "relevant information" in this sentence in the context of the previous line 183-195	Moderate
Page 7, IV.A, CTD Table	Table		IPAC-RS recommends giving the table a title and then referencing it throughout the guidance, where appropriate.	Information or requiring clarification
Page 7, IV.A, CTD Table	Guideline/CTD table describes regular dossier.	Will there be a separate document for special development, for instance continuous manufacturing process, where the regular CTD dossier may not fully fit? If it is not planned to have a separate guideline, a disclaimer could be added that the CTD table can be adapted in case of special development.		Moderate
Pages 7-11 IV.A, CTD Table		More details are requested for S.2.2, S.2.3, S.2.4; P.3.3, P.3.4, P.4. These sections are probably the sections where data limitations could impact the ability to establish the appropriate conditions in initial CTDs. Concrete examples, in particular, for	Some information in these sections goes beyond routine established conditions.	Critical

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		cases of limited data such as breakthrough therapy drugs, could be useful.		
Page 7, IV.A, CTD Table 3.2.S.1.1 Nomenclature	Established Name or Proper Name (for Biologics)	Suggested rewording "Established Name (for Non-biologics) or Proper Name (for Biologics)"	"Established name or Proper Name (for biologics)" is not clear.	Information or requiring clarification
Page 7, IV.A, CTD Table 3.2.S.2.2 Description of Manufacturing Process and Process Controls	Sequential procedural narrative, including certain information in the control strategy that assures process performance and drug substance quality, such as: identification of steps, process controls and parameters (with ranges), equipment and operating conditions (including target settings), input materials, and intermediates.		This seems to indicate there is an expectation that "equipment settings" should be registered. The rationale behind this requirement is unclear and seems to be regulatory creep. IPAC-RS recommends that the reference to "equipment settings" is deleted.	Critical
Page 8, IV.A, CTD Table 3.2.S.2.4 Controls of Critical Steps and Intermediates	Intermediates (e.g., isolated intermediates): Specifications (tests, analytical procedures and acceptance criteria) and hold times	"Hold times" as an established condition seems to be a new requirement. No such requirement is established for drug product. EU describes when the bulk holding time is considered as relevant for DP (i.e. no data to submit for less than 30 days, etc...). It would be helpful to have any US requirement defined, i.e. how to support it.	Hold times are often considered GMP parameters, rather than registered parameters	Moderate

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Page 8 & 11, IV.A, CTD Table 3.2.S.5. and 3.2.P.6 Reference Standards or Materials -	Contains Established Conditions (X) - Qualification protocols for new and existing reference standard materials	Contains Established Conditions (X) - ~~Qualification protocols for new and existing reference standard materials~~ Information on the reference standards or reference materials used for testing of the drug substance should be provided.	Language in table updated as per ICH M4Q (R1). This information may include reference to USP if using USP reference standard or specifications if unique to drug substance. Qualification protocols are not specified per ICH M4Q(R1).	Moderate
Pages 7 & 11; IV.A, CTD Table 3.2.S.6 and 3.2.P.7	"Selected container closure system and controls"	Please explain the phrase "Selected container closure system and controls." For example, please provide examples of changes where submission would not be necessary.	This change will provide greater clarity.	Moderate
Pages 9 and 11, IV.A, CTD Table 3.2.S.7.2 and 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment	3.2.S.7.2: Tests, analytical procedures and acceptance criteria; storage conditions; shelf life; post-approval testing protocol; and commitment(s) 3.2.P.8.2: Tests, analytical procedures and acceptance criteria; storage conditions; shelf life; post-approval testing protocol; and commitment(s)	3.2.S.7.2: ~~Tests, analytical procedures and acceptance criteria; storage conditions; shelf life~~; post-approval testing protocol; and commitment(s) 3.2.P.8.2: ~~Tests, analytical procedures and acceptance criteria; storage conditions; shelf life;~~ post-approval testing protocol; and commitment(s)	Typically the shelf life claims for drug substance and drug product are located in sections S.7.1 and P.8.1 respectively, rather than in sections S.7.2 and P.8.2. As per ICH M4Q(R1): Conclusions with respect to storage conditions and retest date or shelf-life should be provided in 3.2.P.8.1 Stability Summary and Conclusions. Tests, analytical procedures and acceptance criteria should be provided in 3.2.S.4.1 Specification. Tests, analytical procedures and	Critical

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			acceptance criteria should be provided in 3.2.P.5.1 Specification. IPAC-RS recommends that the appropriate changes are made to the table to reflect this.	
Page 10, IV.A, CTD Table 3.2.P.3.3, Description of Manufacturing Process and Process Controls	Sequential procedural narrative, including certain information in the control strategy that assures process performance and product quality, such as: identification of steps, process controls and parameters (with ranges), equipment and operating conditions (including target settings), input materials. For products purporting to be sterile, the control strategy should include details regarding the product or component sterilization methods and/or aseptic manufacturing operations		This seems to indicate that there is an expectation that "equipment settings" should be registered. The rationale behind this requirement is unclear and seems to be regulatory creep. IPAC-RS recommends that the reference to "equipment settings" is deleted.	Critical
Page 10, IV.A 3.2.P.3.3 Description of Manufacturing Process and Process Controls	Sequential procedural narrative, including certain information in the control strategy that assures process performance and product quality, such as: identification of steps, process controls and parameters (with ranges), equipment and operating conditions (including target settings), input materials For products purporting to be		There is an expectation to describe the sterilization conditions and aseptic operations as an established condition, but minimal guidance on level of information needed is given. Further clarification on the expected level of description of aseptic processing would be helpful, e.g. Detail around design elements, but not specifying GMP aspects.	Critical

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	sterile, the control strategy should include details regarding the product or component sterilization methods and/or aseptic manufacturing operations			
Page 12, IV.A 3.2.A.1 Facilities and Equipment	X	Suggested Text in the Contains Established Conditions column and row for 3.2.A.1: "X (<u>for Biotech products ONLY)".</u>	Facilities and Equipment should only be considered established conditions for Biotech products (see M4Q: The CTD-Quality Guidance for Industry, Aug 2001). Therefore, IPAC-RS recommends that established condition indications should be clarified with a footnote or include a parenthetic phrase to define specific application.	Critical
Page 12, IV.B / 215-218	We also recommend that this information be provided in a tabular format, and include a brief description or identification of the established condition, with a reference to its specific location(s) in Module 3 of the CTD	The level of granularity and detail on the established condition is not clear. Additional examples on the format of the tabular summary would be beneficial (actual cases).	There is concern that the length and detail of such tabular summaries, as well as the hyperlinking into relevant sections of Module 3 CTD sections, could lead to submission publication and electronic transmission and maintenance challenges. As mentioned in the FDA draft guideline, section IV.B., the CTD table indicates those CTD sections which typically would contain established conditions, but do not represent established conditions in its entirety. Thus an overview table could become extremely long in order to clearly show which elements are considered established conditions. One example	Critical

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			of extensive listing requirements would be the information contained in A.1 “Facilities and Equipment,” which also includes floor plans.	
Page 12, IV.B / 223-225	Demonstration of risk mitigation within the application can allow for greater operational flexibility for certain parameters typically considered established conditions.	Clarify that product and process understanding and risk management approaches would allow for certain parameters to be considered non-critical. Further clarify in which sections these “risk mitigation” actions should be included and associated with established conditions.	It is assumed that “risk mitigation” in this context refers to demonstrating that certain parameters typically considered to be established conditions are non-critical, can allow for greater operation flexibility. Further clarification of this important point is needed. In which section are "risk mitigation" actions submitted, and how could these be linked to the ‘established conditions’ tabular format (if linking is needed)?	Critical
Page 13 IV.B / 236-238	For legacy products an extensive body of process knowledge and experience on control strategy is available. Therefore no retrospective delineation of established conditions should be necessary.	Change to: “For legacy products retrospective delineation of established conditions is not mandatory. The applicant or sponsor may determine whether delineation of established conditions is appropriate.”	Guidance should make clear that, for legacy products, there is no compulsory requirement to submit a tabular summary of established conditions in supplemental submissions until such time that the Applicant formally defines them (per the forthcoming process FDA plans to develop as noted). This should also be reiterated (as footnote) in Section IV.C.	Critical
Pages 13 – 14, IV.B / 258-273	When new information learned during commercial manufacturing leads to the addition or modification of one or more established conditions, the		This paragraph describes the process for changing, or removing, an established condition by either supplement or annual report, using the submission type as defined in	Moderate

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	applicant should provide an updated summary of the established conditions and supportive information (e.g., validation data, batch analysis) for any new or modified established conditions in a manufacturing supplement (i.e., if a supplement is needed for the modification) or the next annual report. Alternatively, if it is determined that an established condition is no longer necessary to assure process performance and quality of the product, the applicant may remove an established condition by submitting a supplement or annual report, where the submission type is based on the recommendations found in FDA regulations and post-approval changes guidance documents or in an approved protocol. The submission should clearly explain how this determination was made, including associated commercial-scale data, studies, risk assessments, new scientific knowledge used to support this determination, and the elements of the control strategy that will provide adequate or improved control. For example, if on-line, real-time attribute monitoring is		post-approval change guidance. It is unclear how the submission type would be determined to support removal of an established condition. Specifically, it is unclear which established conditions could be removed via Annual Report as the basis for justifying such a proposal would involve a review of the risk mitigation strategy, or design of experiments.	

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	implemented post-approval for a particular unit operation, it may be acceptable to designate the on-line monitoring (e.g., NIR analysis) as an established condition, while removing the inputs and process parameters for the unit operation from the established conditions.			